10/698,928
~~10/698,924~~

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1201txs

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 25	CA/CAPLUS - Russian Agency for Patents and Trademarks (ROSPATENT) added to list of core patent offices covered
NEWS	4	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	5	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	6	FEB 28	MEDLINE/LMEDLINE reloaded
NEWS	7	MAR 02	GBFULL: New full-text patent database on STN
NEWS	8	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	9	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	10	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	11	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	12	MAR 22	PATDPASPC - New patent database available
NEWS	13	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	14	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	15	APR 04	EMBASE - Database reloaded and enhanced
NEWS	16	APR 18	New CAS Information Use Policies available online
NEWS	17	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	18	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	19	MAY 23	GBFULL enhanced with patent drawing images
NEWS	20	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	21	MAY 26	STN User Update to be held June 6 and June 7 at the SLA 2005 Annual Conference

NEWS EXPRESS JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

10/698,928
~~10/698,924~~

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* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:26:40 ON 01 JUN 2005

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.73	2.73

FILE 'REGISTRY' ENTERED AT 16:34:24 ON 01 JUN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 30 MAY 2005 HIGHEST RN 851366-70-6
DICTIONARY FILE UPDATES: 30 MAY 2005 HIGHEST RN 851366-70-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

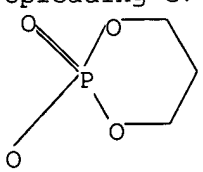
Please note that search-term pricing does apply when conducting SmartSELECT searches.

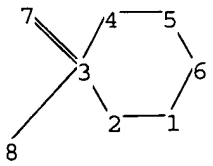
****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Crossover limits have been increased. See HELP CROSSOVER for details.

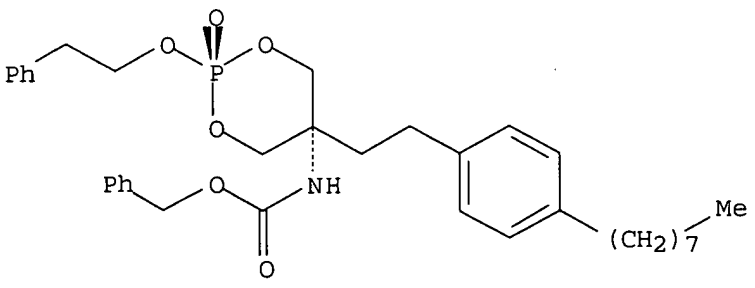
Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10698924.str





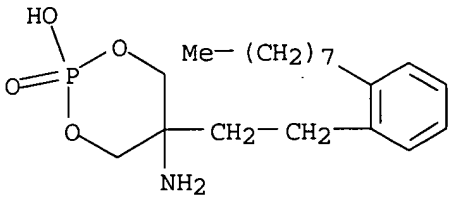
```
chain nodes :
7  8
ring nodes :
1  2  3  4  5  6
chain bonds :
3-7  3-8
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6
exact/norm bonds :
3-7  3-8
exact bonds :
1-2  1-6  2-3  3-4  4-5  5-6
isolated ring systems :
containing 1 :


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:CLASS  8:CLASS



L1      STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 16:34:46 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    469 TO ITERATE

100.0% PROCESSED     469 ITERATIONS                          50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          8081 TO    10679
PROJECTED ANSWERS:             1299 TO     2461

L2           50 SEA SSS SAM L1

=> d scan

L2   50 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   Carbamic acid, [cis-5-[2-(4-octylphenyl)ethyl]-2-oxido-2-(2-phenylethoxy)-
     1,3,2-dioxaphosphorinan-5-yl]-, phenylmethyl ester (9CI)
MF   C35 H46 N O6 P

Relative stereochemistry.
```



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

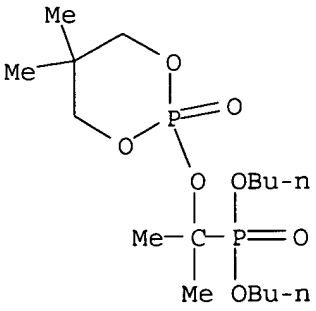
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):2

L2 50 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1,3,2-Dioxaphosphorinan-5-amine, 2-hydroxy-5-[2-(2-octylphenyl)ethyl]-, 2-oxide (9CI)
MF C19 H32 N O4 P



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 50 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Phosphonic acid, [1-[(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphorinan-2-yl)oxy]-1-methylethyl]-, dibutyl ester (9CI)
MF C16 H34 O7 P2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

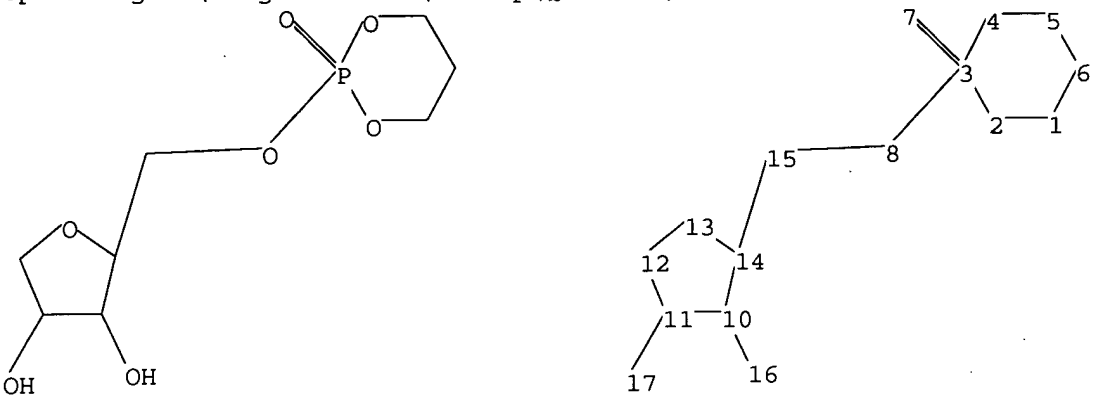
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> s l1 ful
FULL SEARCH INITIATED 16:35:54 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 9915 TO ITERATE

100.0% PROCESSED 9915 ITERATIONS 1678 ANSWERS
SEARCH TIME: 00.00.02

L3 1678 SEA SSS FUL L1

=>
Uploading C:\Program Files\Stnexp\Queries\106989241.str



chain nodes :
7 8 15 16 17
ring nodes :
1 2 3 4 5 6 10 11 12 13 14
chain bonds :
3-7 3-8 8-15 10-16 11-17 14-15
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 10-11 10-14 11-12 12-13 13-14
exact/norm bonds :
3-7 3-8 8-15 10-16 11-17
exact bonds :
1-2 1-6 2-3 3-4 4-5 5-6 10-11 10-14 11-12 12-13 13-14 14-15
isolated ring systems :
containing 1 : 10 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS

L4 STRUCTURE UPLOADED

=> s l4
SAMPLE SEARCH INITIATED 16:39:17 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 6 TO ITERATE

100.0% PROCESSED 6 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 6 TO 266
PROJECTED ANSWERS: 0 TO 0

L5 0 SEA SSS SAM L4

=> s l4 ful
FULL SEARCH INITIATED 16:39:28 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 279 TO ITERATE

100.0% PROCESSED 279 ITERATIONS 23 ANSWERS
SEARCH TIME: 00.00.01

L6 23 SEA SSS FUL L4

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	325.67	328.40

FILE 'CAPLUS' ENTERED AT 16:39:35 ON 01 JUN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 1 Jun 2005 VOL 142 ISS 23
FILE LAST UPDATED: 31 May 2005 (20050531/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l6
L7 9 L6

=> d l7 ibib hitstr abs 1-9

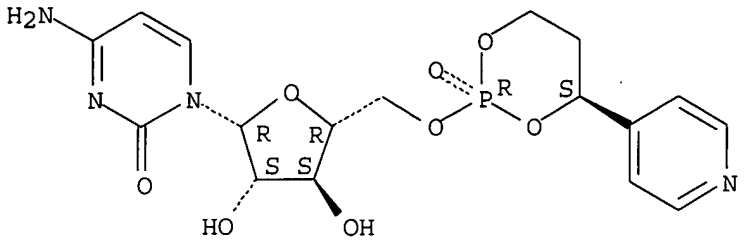
L7 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:144430 CAPLUS
DOCUMENT NUMBER: 142:397467
TITLE: Liver-targeted drug delivery using HepDirect prodrugs
AUTHOR(S): Erion, Mark D.; Van Poelje, Paul D.; MacKenna, Deidre A.; Colby, Timothy J.; Montag, Annika C.; Fujitaki, James M.; Linemeyer, David L.; Bullough, David A.
CORPORATE SOURCE: Metabasis Therapeutics, Inc., San Diego, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 312(2), 554-560
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **685111-92-6**, MB 07133

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liver-targeted drug delivery using HepDirect prodrugs)

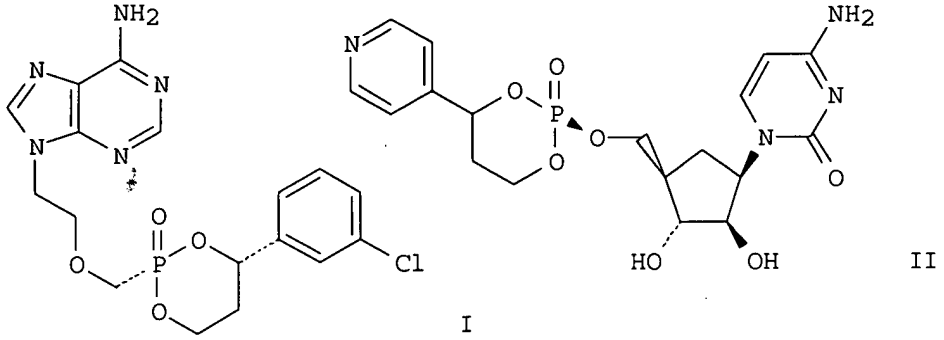
RN 685111-92-6 CAPLUS

CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



I II

AB Targeting drugs to specific organs, tissues, or cells is an attractive strategy for enhancing drug efficacy and reducing side effects. Drug carriers such as antibodies, natural and man-made polymers, and labeled liposomes are capable of targeting drugs to blood vessels of individual tissues but often fail to deliver drugs to extravascular sites. An alternative strategy is to use low mol. weight prodrugs that distribute throughout the body but cleave intracellularly to the active drug by an organ-specific enzyme. Here we show that a series of phosphate and phosphonate prodrugs, called HepDirect prodrugs, results in liver-targeted drug delivery following a cytochrome P 450-catalyzed oxidative cleavage reaction inside hepatocytes. Liver targeting was demonstrated in rodents for MB06866 (I) (remofovir), a Hep-Direct prodrug of the nucleotide analog adefovir (PMEA), and MB07133 (II), a HepDirect prodrug of cytarabine (araC) 5'-monophosphate. Liver targeting led to higher levels of the biol. active form of PMEA and araC in the liver and to lower levels in the most toxicol. sensitive organs. Liver targeting also confined production of the prodrug byproduct, an aryl vinyl ketone, to hepatocytes. Glutathione within the hepatocytes rapidly reacted with the byproduct to form a glutathione conjugate. No byproduct-related toxicity was observed in hepatocytes or animals treated with HepDirect prodrugs. A 5-day safety

study in mice demonstrated the toxicol. benefits of liver targeting. These findings suggest that HepDirect prodrugs represent a potential strategy for targeting drugs to the liver and achieving more effective therapies against chronic liver diseases such as hepatitis B, hepatitis C, and hepatocellular carcinoma.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

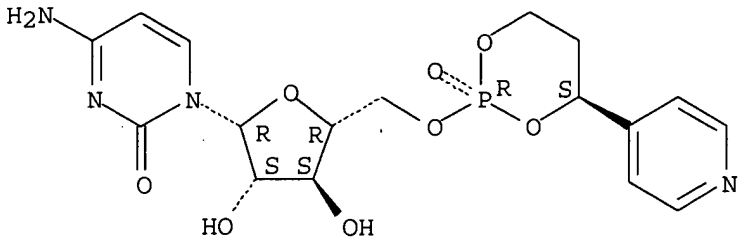
L7 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:392312 CAPLUS
DOCUMENT NUMBER: 140:375424
TITLE: Preparation of nucleotides cytarabine monophosphate prodrugs as antitumor and antiviral agents
INVENTOR(S): Boyer, Serge; Erion, Mark D.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 46 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004092476	A1	20040513	US 2003-698928	20031031
WO 2004041837	A1	20040521	WO 2003-US34690	20031031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2004041834	A2	20040521	WO 2003-US34709	20031031
WO 2004041834	A3	20040701		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004192651	A1	20040930	US 2003-698924	20031031
PRIORITY APPLN. INFO.:			US 2002-423211P	P 20021031
			US 2002-423259P	P 20021031

IT **685111-92-6P 685112-02-1P**
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nucleotides cytarabine monophosphate prodrugs as antitumor and antiviral agents)
RN 685111-92-6 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-

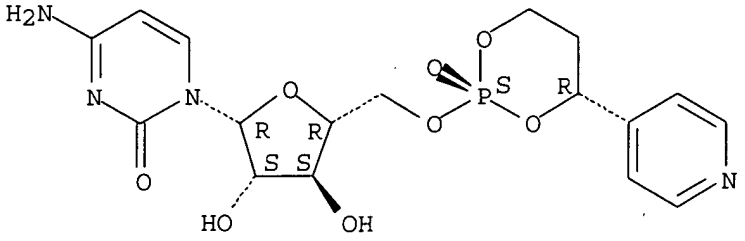
dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 685112-02-1 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2S,4R)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

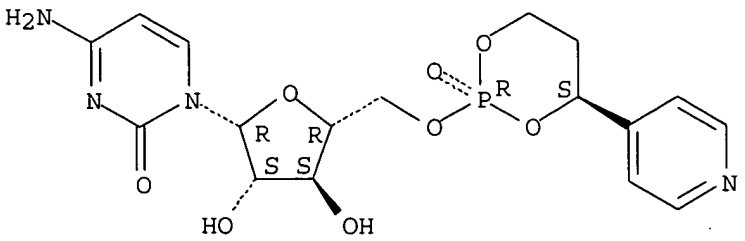


IT **685111-96-0P 685111-97-1P 685111-98-2P**
685111-99-3P 685112-00-9P
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nucleotides cytarabine monophosphate prodrugs as antitumor and antiviral agents)
RN 685111-96-0 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-, mono[(1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate] (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 685111-92-6
CMF C17 H21 N4 O8 P

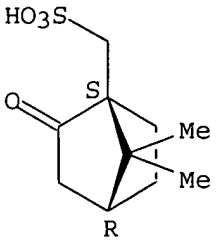
Absolute stereochemistry.



CM 2

CRN 3144-16-9
CMF C10 H16 O4 S

Absolute stereochemistry. Rotation (+).

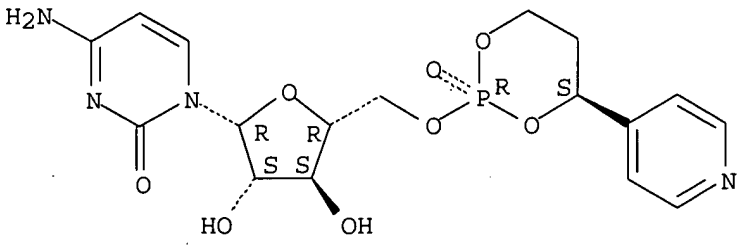


RN 685111-97-1 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-, (2Z)-2-butenedioate (2:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 685111-92-6
CMF C17 H21 N4 O8 P

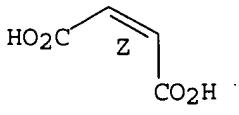
Absolute stereochemistry.



CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.

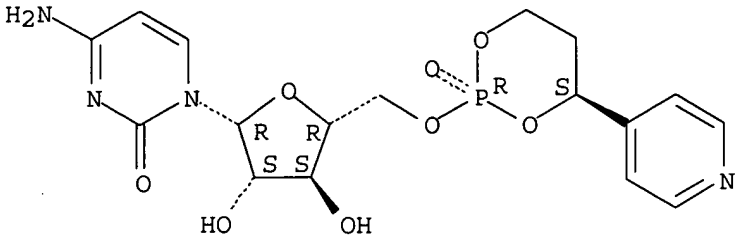


RN 685111-98-2 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-, sulfate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

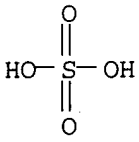
CRN 685111-92-6
CMF C17 H21 N4 O8 P

Absolute stereochemistry.



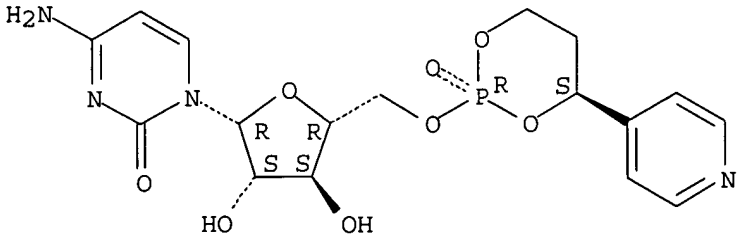
CM 2

CRN 7664-93-9
CMF H2 O4 S



RN 685111-99-3 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



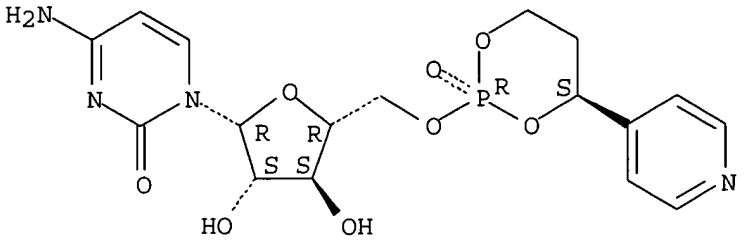
● HCl

RN 685112-00-9 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 685111-92-6
CMF C17 H21 N4 O8 P

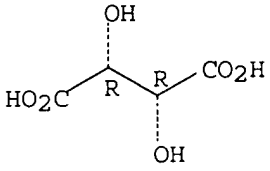
Absolute stereochemistry.



CM 2

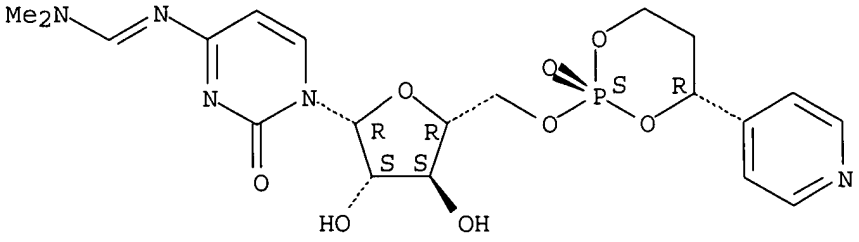
CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

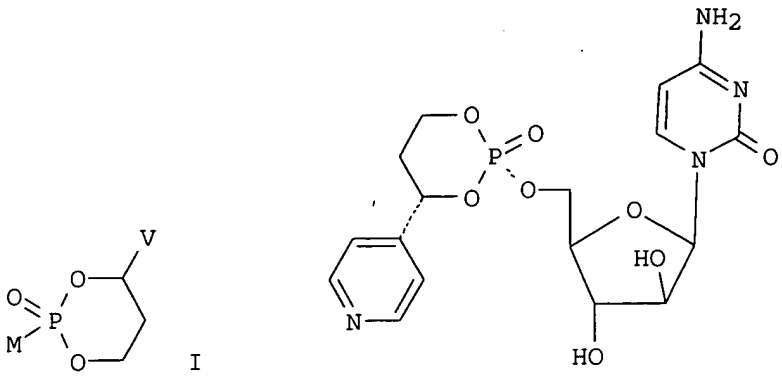


IT **685111-95-9P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nucleotides cytarabine monophosphate prodrugs as antitumor and antiviral agents)
RN 685111-95-9 CAPLUS
CN Methanimidamide, N'-[1,2-dihydro-1-[5-O-[(2S,4R)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]-2-oxo-4-pyrimidinyl]-N,N-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



GI

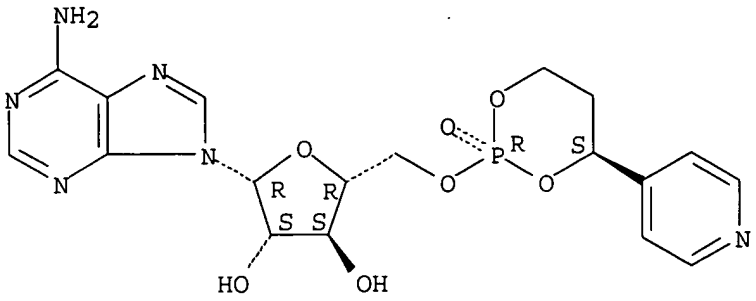


I II

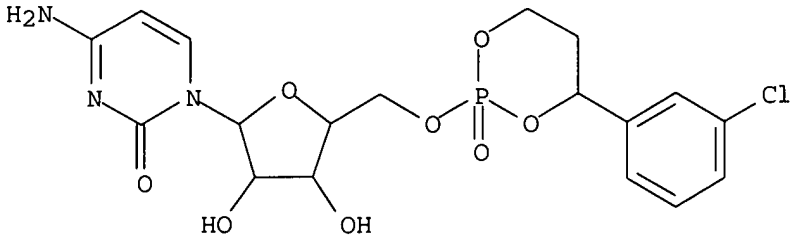
AB Nucleotides cytarabine monophosphate I, wherein M and V are cis to one another and MH is cytarabine; the 5'-oxygen of said cytarabine is attached to the phosphorus; V is 4-pyridyl; and pharmaceutically acceptable prodrugs and salts thereof. Thus, nucleotide II was prepared and tested in mice as antitumor and antiviral agents. Kinetic parameters of activation of title compds. in human liver microsomes are described. Activation of prodrugs in vivo was measured after bolus i.p. administration to mice. Compds. were administered at 100 mg (cytarabine equivalent)/kg using a single IP injection.

L7 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:267894 CAPLUS
DOCUMENT NUMBER: 140:417194
TITLE: Design, Synthesis, and Characterization of a Series of Cytochrome P450 3A-Activated Prodrugs (HepDirect Prodrugs) Useful for Targeting Phosph(on)ate-Based Drugs to the Liver
AUTHOR(S): Erion, Mark D.; Reddy, K. Raja; Boyer, Serge H.; Matelich, Michael C.; Gomez-Galeno, Jorge; Lemus, Robert H.; Ugarkar, Bheemarao G.; Colby, Timothy J.; Schanzer, Juergen; van Poelje, Paul D.
CORPORATE SOURCE: Departments of Medicinal Chemistry and Biochemistry, Metabasis Therapeutics, Inc., San Diego, CA, 92121, USA
SOURCE: Journal of the American Chemical Society (2004), 126(16), 5154-5163
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:417194
IT **693223-02-8P 693227-28-0P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design, synthesis, and characterization of cytochrome P450 3A-activated prodrugs (HepDirect prodrugs) useful for targeting phosph(on)ate-based drugs to liver)
RN 693223-02-8 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-[(2R,4S)-2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

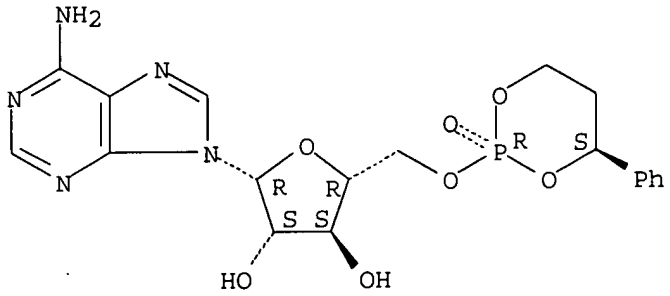


RN 693227-28-0 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[[rel-(2R,4S)]-4-(3-chlorophenyl)-2-oxido-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)



IT **693223-01-7P 693223-03-9P 693223-04-0P 693227-29-1P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design, synthesis, and characterization of cytochrome P450 3A-activated prodrugs (HepDirect prodrugs) useful for targeting phosph(on)ate-based drugs to liver)
RN 693223-01-7 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-[(2R,4S)-2-oxido-4-phenyl-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

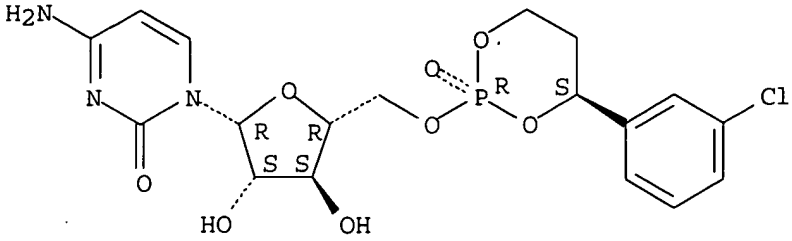
Absolute stereochemistry.



RN 693223-03-9 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2R,4S)-4-(3-chlorophenyl)-2-oxido-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX

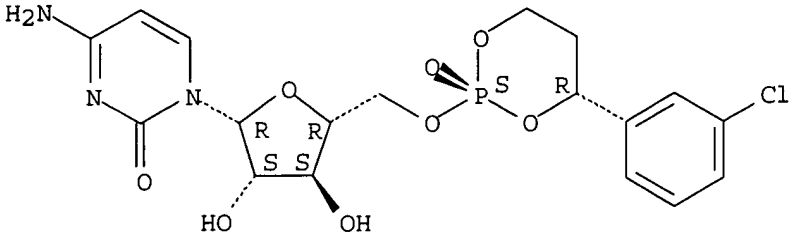
NAME)

Absolute stereochemistry.

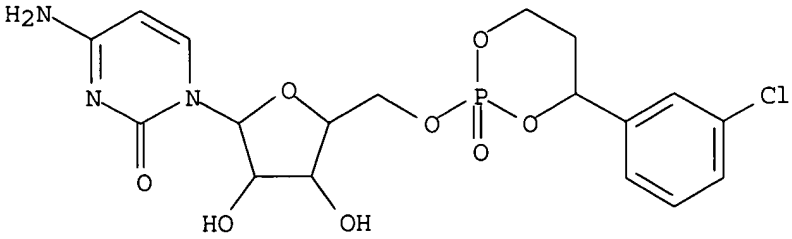


RN 693223-04-0 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[(2S,4R)-4-(3-chlorophenyl)-2-oxido-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 693227-29-1 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[5-O-[[rel-(2R,4R)]-4-(3-chlorophenyl)-2-oxido-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)



AB A new class of phosphate and phosphonate prodrugs, called HepDirect prodrugs, is described that combines properties of rapid liver cleavage with high plasma and tissue stability to achieve increased drug levels in the liver. The prodrugs are substituted cyclic 1,3-propanyl esters designed to undergo an oxidative cleavage reaction catalyzed by a cytochrome P450 (CYP) expressed predominantly in the liver. Reported herein is the discovery of a prodrug series containing an aryl substituent at C4 and its use for the delivery of nucleoside-based drugs to the liver. Prodrugs of 5'-monophosphates of vidarabine, lamivudine (3TC), and cytarabine as well as the phosphonic acid adefovir were shown to cleave following exposure to liver homogenates and exhibit good stability in blood and other tissues. Prodrug cleavage required the presence of the

aryl group in the cis-configuration, but was relatively independent of the nucleoside and absolute stereochem. at C4. Mechanistic studies suggested that prodrug cleavage proceeded via an initial CYP3A-catalyzed oxidation to an intermediate ring-opened monoacid, which subsequently was converted to the phosph(on)ate and an aryl vinyl ketone by a β-elimination reaction. Studies in primary rat hepatocytes and normal rats comparing 3TC and the corresponding HepDirect prodrug demonstrated the ability of these prodrugs to effectively bypass the rate-limiting nucleoside kinase step and produce higher levels of the biol. active nucleoside triphosphate.

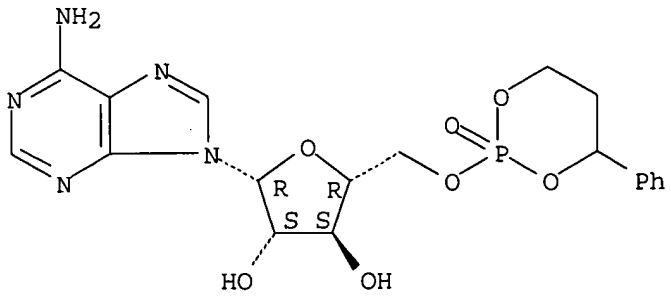
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:808252 CAPLUS
DOCUMENT NUMBER: 135:348869
TITLE: Prodrugs phosphorus-containing compounds and pharmacodynamic action
INVENTOR(S): Erion, Mark D.; Reddy, K. Raja; Robinson, Edward D.; Ugarkar, Bheemarao G.
PATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
SOURCE: U.S., 92 pp., Cont.-in-part of U.S. Ser. No. 263,976. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6312662	B1	20011106	US 1999-392352		19990908
US 2002052345	A1	20020502	US 2001-978454		20011015
PRIORITY APPLN. INFO.:			US 1998-77164P	P	19980306
			US 1998-77165P	P	19980306
			US 1999-263976	A2	19990305
			US 1999-392352	A1	19990908

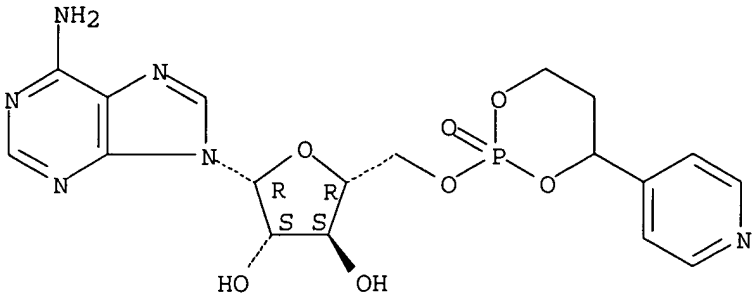
OTHER SOURCE(S): MARPAT 135:348869
IT **240434-53-1P 240434-54-2P 240434-56-4P 240434-57-5P 240487-27-8P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(preparation and pharmacodynamics of phosphorus-containing prodrugs)
RN 240434-53-1 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-(2-oxido-4-phenyl-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



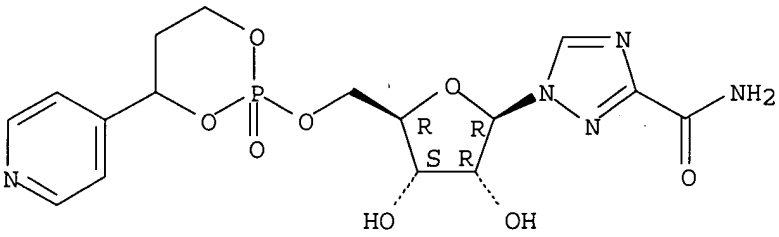
RN 240434-54-2 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-[2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



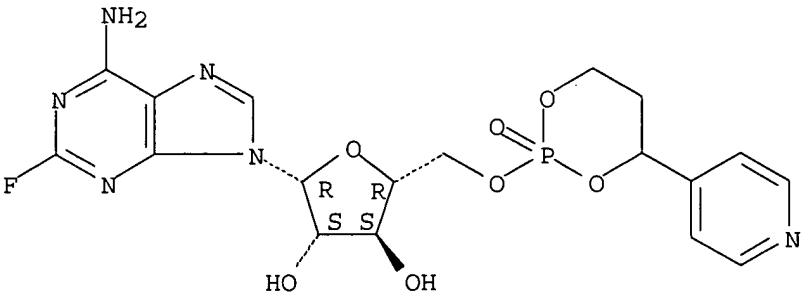
RN 240434-56-4 CAPLUS
CN 1H-1,2,4-Triazole-3-carboxamide, 1-[5-O-[2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-ribofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



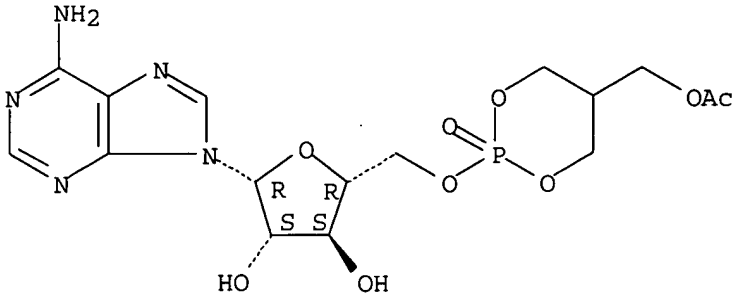
RN 240434-57-5 CAPLUS
CN 9H-Purin-6-amine, 2-fluoro-9-[5-O-[2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 240487-27-8 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-[5-[(acetyloxy)methyl]-2-oxido-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB The present invention is directed towards novel prodrugs of phosphate, phosphonate, and phosphoramidate compds. which in their active form have a phosphate, phosphonate, or phosphoramidate group, to their preparation, to their synthetic intermediates, and to their uses. More specifically, the invention relates to the area of substituted cyclic 1,3-propanyl phosphate, phosphonate and phosphoramidate esters.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:576934 CAPLUS
DOCUMENT NUMBER: 131:185194
TITLE: Preparation of cyclic nucleotides as FBPase inhibitor prodrugs
INVENTOR(S): Erion, Mark D.; Reddy, K. Raja; Robinson, Edward D.
PATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 240 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

10/31/ 2002
9/10/ 1999
> 3 yrs

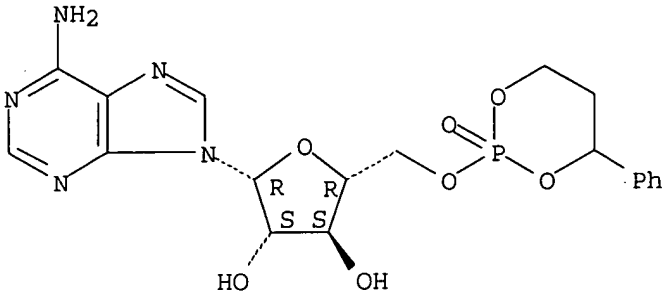
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9945016	A2	19990910	WO 1999-US4908		19990305
WO 9945016	A3	20000615			
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2322487	AA	19990910	CA 1999-2322487		19990305
AU 9930699	A1	19990920	AU 1999-30699		19990305
AU 767599	B2	20031120			
EP 1060182	A2	20001220	EP 1999-912300		19990305
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002505333	T2	20020219	JP 2000-534558		19990305
PRIORITY APPLN. INFO.:			US 1998-77164P	P	19980306
			US 1998-77165P	P	19980306
			WO 1999-US4908	W	19990305

OTHER SOURCE(S): MARPAT 131:185194
IT **240434-53-1P 240434-54-2P 240434-56-4P**

240434-57-5P 240487-27-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic nucleotides as FBPase inhibitor prodrugs)

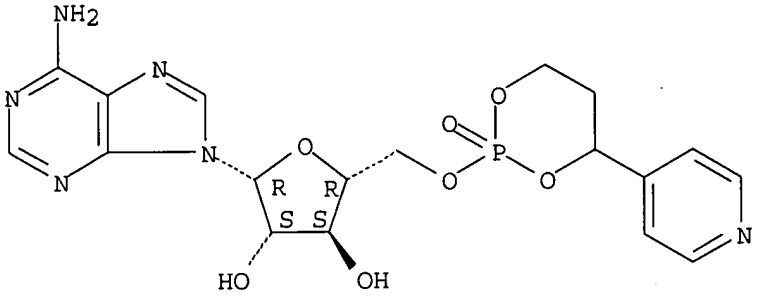
RN 240434-53-1 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-(2-oxido-4-phenyl-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



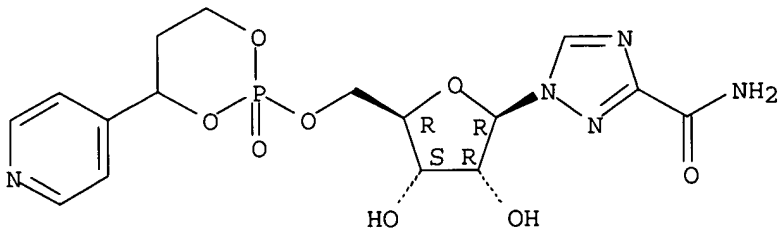
RN 240434-54-2 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-[2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 240434-56-4 CAPLUS
CN 1H-1,2,4-Triazole-3-carboxamide, 1-[5-O-[2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-ribofuranosyl]- (9CI) (CA INDEX NAME)

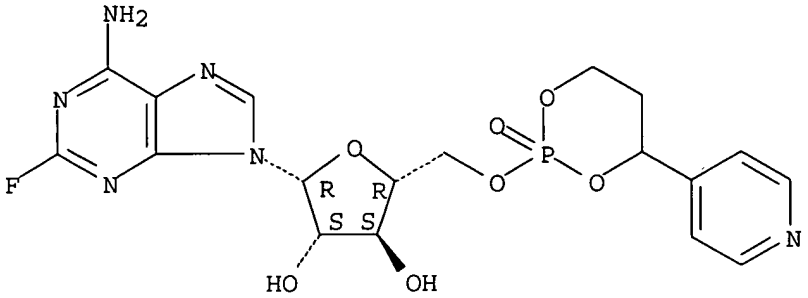
Absolute stereochemistry.



RN 240434-57-5 CAPLUS

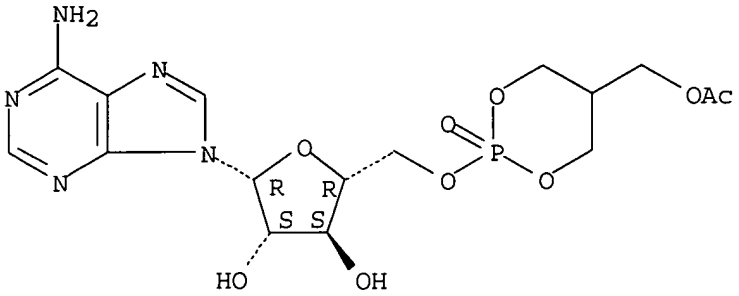
CN 9H-Purin-6-amine, 2-fluoro-9-[5-O-[2-oxido-4-(4-pyridinyl)-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

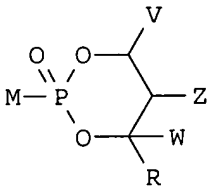


RN 240487-27-8 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-[5-[(acetyloxy)methyl]-2-oxido-1,3,2-dioxaphosphorinan-2-yl]-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



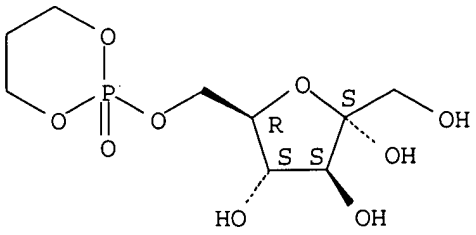
I

AB Prodrugs of phosphorus-containing nucleotides I, wherein V is selected from the group consisting of H, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R9; or together V and Z are connected via 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or together V and Z are connected via 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the oxygen attached to the phosphorus. Together V and W are connected via 3 carbon atoms to form an optionally substituted cyclic group containing 6

carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; W and R are independently selected from the group consisting of H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R9. Z is selected from the group consisting of -CHR2OH, -CHR2OC(O)R3, -CHR2OC(S)R3, -CHR2OC(S)OR3, -CHR2OC(O)SR3, -CHR2OCO2R3, -OR2, -SR2, -CHR2N3, -CH2aryl, -CH(aryl)OH, -CH(CH=CR22)OH, -CH(C.tplbond.CR2)OH, -R2, -NR22, -OCOR3, -OCO2R3, -SCOR3, -SCO2R3, -NHCOR2, -NHCO2R3, -CH2NHaryl, (CH2)p-OR2, and (CH2)p-SR2; -R2 is an R3 or -H; R3 is selected from the group consisting of alkyl, aryl, aralkyl, and alicyclic; and R9 is selected from the group consisting of alkyl, aralkyl, and alicyclic; p is an integer from 2 to 3. With the proviso that (a) V, Z, W, and R are not all -H; and (b) when Z is -R2, then at least one of V and W is not -H, or -R9; and M is selected from the group that attached to PO32-, P2O63-, or P3O94- is biol. active in vivo, and that is attached to the phosphorus in I via a carbon, oxygen, or nitrogen atom; and pharmaceutically acceptable prodrugs and salts thereof. Thus, cyclic nucleotide I (M = adenine-9-β-D-arabinofuranos-5'-yl; V = 4-pyridyl; Z = W = R = H) was prepared and tested as prodrug human liver FBPase inhibitor (EC50 < 10 μM).

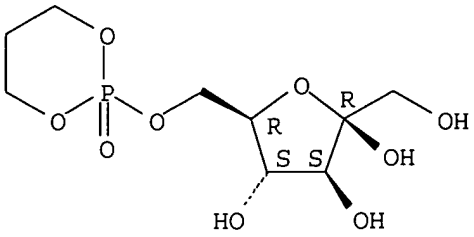
L7 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:559534 CAPLUS
DOCUMENT NUMBER: 115:159534
TITLE: Synthesis of partially-protected D-fructofuranoses and D-fructose-6-phosphates
AUTHOR(S): Ayral-Kaloustian, Semiramis; Floyd, M. Brawner, Jr.
CORPORATE SOURCE: Med. Res. Div., Am. Cyanamid Co., Pearl River, NY, 10965, USA
SOURCE: Carbohydrate Research (1991), 214(1), 187-92
CODEN: CRBRAT; ISSN: 0008-6215
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 115:159534
IT **136215-66-2P 136215-67-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 136215-66-2 CAPLUS
CN α-D-Fructofuranose, 6-O-(2-oxido-1,3,2-dioxaphosphorinan-2-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

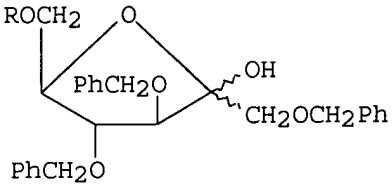


RN 136215-67-3 CAPLUS
CN β-D-Fructofuranose, 6-O-(2-oxido-1,3,2-dioxaphosphorinan-2-yl)- (9CI) (CA INDEX NAME)

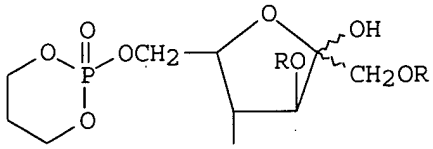
Absolute stereochemistry.



GI



I

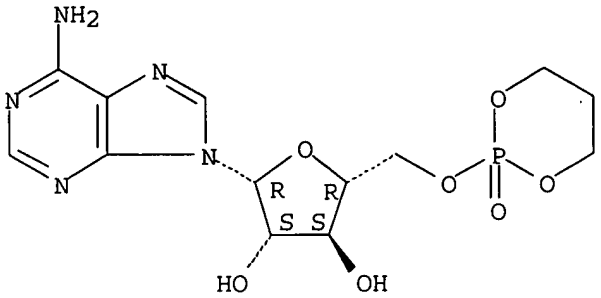


III

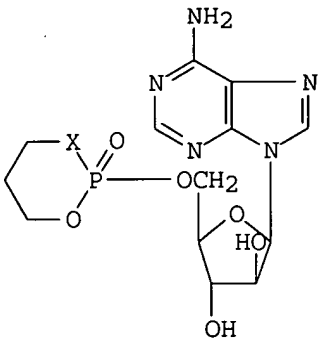
AB A new synthesis of fructofuranoses I [R = H (II), CH2Ph] from 2,3,5-tri-O-benzyl-D-arabinonolactone, is reported. Phosphorylation of II with 2-chloro-1,3,2-dioxaphosphorinane 2-oxide gave fructofuranose phosphates III.

L7 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:488160 CAPLUS
DOCUMENT NUMBER: 103:88160
TITLE: Synthesis and biological evaluation of 9-[5'-(2-oxo-1,3,2-oxazaphosphorinan-2-yl)-β-D-arabinosyl]adenine and 9-[5'-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinosyl]adenine: potential neutral precursors of 9-[β-D-arabinofuranosyl]adenine 5'-monophosphate
AUTHOR(S): Farquhar, David; Smith, Ronald
CORPORATE SOURCE: Syst. Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SOURCE: Journal of Medicinal Chemistry (1985), 28(9), 1358-61
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 103:88160
IT **78000-58-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation, enzymic degradation, and antitumor activity of)
RN 78000-58-5 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-(2-oxido-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



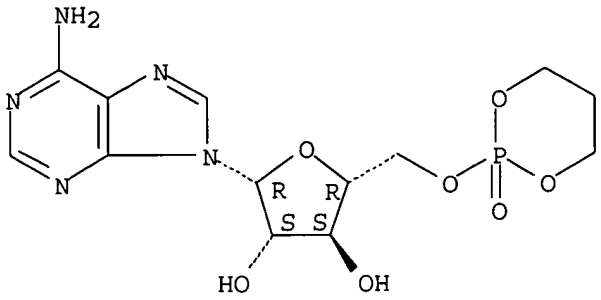
I, X=NH
II, X=O

AB Title 5'-cyclic nucleotides I and II were prepared by reaction of 9-(β-D-arabinofuranosyl)adenine with POCl3 and HO(CH2)3XH. I consisted of a mixture of diastereomers, while II was enantiomerically homogeneous. Both I and II were resistant to degradation by 5'-nucleotidase, alkaline phosphatase, venom phosphodiesterase, crude snake venom, adenosine deaminase, and adenylate deaminase. Neither compound was significantly biotransformed by mouse hepatic microsomal prepns. in the presence of an NADPH-generating system. I was marginally effective at prolonging the life span of mice bearing P-388 leukemia; II however, was inactive.

L7 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1981:425475 CAPLUS
DOCUMENT NUMBER: 95:25475
TITLE: Mass spectral characterization of some nucleoside phosphates and phosphoramidates
AUTHOR(S): Smith, Ronald G.; Farquhar, David
CORPORATE SOURCE: Syst. Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SOURCE: Journal of Heterocyclic Chemistry (1980), 17(8), 1659-61
CODEN: JHTCAD; ISSN: 0022-152X
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **78000-58-5D**, trimethylsilyl derivative
RL: PRP (Properties)
(mass spectrum of)

RN 78000-58-5 CAPLUS
CN 9H-Purin-6-amine, 9-[5-O-(2-oxido-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinofuranosyl]- (9CI) (CA INDEX NAME)

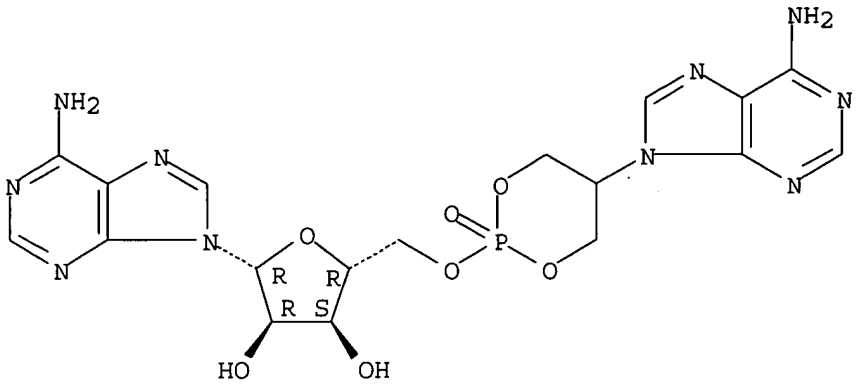
Absolute stereochemistry.



AB Seven new synthetic nucleotide analogs were characterized as their trimethylsilyl derivs. by determining their electron impact mass spectra. These spectra are consistent with their expected structures, most of which possess a cyclic phosphate or phosphoramidate group.

L7 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1976:90474 CAPLUS
DOCUMENT NUMBER: 84:90474
TITLE: Oligonucleotidic compounds. LVI. Synthesis and CD spectrum of 5-(adenin-9-yl)-2-(adenosin-5'-yloxy)-2-oxo-1,3,2-dioxaphosphorinane (adenosine 5'-phosphate 9-(1',3'-dihydroxy-2'-propyl)adenine 1',3'-cyclic ester)
AUTHOR(S): Mikhailov, S. N.; Smrt, Jiri
CORPORATE SOURCE: Inst. Org. Chem. Biochem., Czech. Acad. Sci., Prague, Czech.
SOURCE: Collection of Czechoslovak Chemical Communications (1975), 40(10), 3080-5
CODEN: CCCCAK; ISSN: 0010-0765
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **58377-27-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 58377-27-8 CAPLUS
CN Adenosine, 5'-O-[5-(6-amino-9H-purin-9-yl)-2-oxido-1,3,2-dioxaphosphorinan-2-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI For diagram(s), see printed CA Issue.

AB A mixture of adenine, DMF, and NaH heated at 90° 1 hr, treated with p-MeC6H4SO2OCH(CH2OCPh3)2, and heated at 90° 50 hr gave I (R1 = H, R2 = Ph3C)(II) which was refluxed in 80% aqueous AcOH to yield I (R1 = R2 = H). II was benzoylated with BzCl and C5H5N and then detritylated in refluxing 90% aqueous AcOH to give I (R1 = Bz, R2 = H). Reaction of this compound with 2',3'-di-O-acetyl-N6-acetyladenosine 5'-phosphate in the presence of 2,3,5-(Me2CH)3C6H2SO2Cl gave III, which was deblocked with NH3/MeOH to give the title compound

=> log y

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CA SUBSCRIBER PRICE	-6.57	-6.57

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